REMARKS

In this Amendment, claims 1-15, 17-24, 26-33, 35-39, 42-45, 49-57, and 59-61 have been canceled, claims 16, 25, 34, 40, 46-48, and 58 have been amended, and new claim 62 has been added. In light of the amendments to the pending claims, Applicants respectfully request reconsideration and allowance of the pending and new claims.

The amendment to the title merely corrects a typographical error. It is supported throughout the specification by the use of the term "NAP1L2" and does not add new matter.

New claim 62 is supported by original claim 24 and does not add new matter.

Rejections under 35 U.S.C. § 101

The Office rejected claims 15-19, 22, 24, 34, 40, 46, 48, 56-58, and 60-61 as being directed to non-statutory subject matter, because it asserted that a "recombinant polynucleotide" or "polynucleotide" encompasses all naturally occurring polynucleotides or gene sequences. *See* Paper No. 15, item 2. Applicants have amended pending claims 25, 46, and 47 to recite a "purified polynucleotide".

The Office also rejected these claims because it asserted that the term "a neural/eukaryotic cell" or "recombinant neural cell" would encompass an entire human organism. *See* Paper No. 15 at 4, lines 5-7. Applicants have amended claims 34, 40, and 48 to recite "an purified neural/eukaryotic cell". In light of these amendments, Applicants respectfully request that the rejections be withdrawn.

The Office also rejected claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58, and 60-61 as not being supported by either a credible asserted utility or a well-established utility. See Paper No. 15, item 3. The Office asserted that the specification describes

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the role of *Nap1l2* in the development of the neural system but does not describe a specific utility because many other genes may be involved in neural system development. The Office further asserted that

> no specific utility exists for the instant claimed gene sequences, because no specific biological activity nor specific "developmental defect" is described within the specification that is specifically associated with any nucleic acid transcribed by the promoter polynucleotide sequence of SEQ ID NO: 4.

Paper No. 15 at 5, lines 1-3.

Applicants traverse this rejection and assert that contrary to the Office's conclusions, specific biological activities and specific developmental defects are described in the specification. As explained in the Summary of the Invention:

> A targeted deletion of the X-linked *Nap1l2* gene in male ES cells, which would be expected to lead to the complete absence of the NAP1L2 protein, was created. In close agreement with the first detectable signs of *Nap1l2* expression at day 9.5, the mutation resulted in embryonic lethality from mid-gestation onwards. Surviving embryos derived from ES cell-morula aggregates exhibited neural tube closure defects, associated with marked overproduction of neuronal tissues.

Specification at 3, lines 10-18. More specifically, the specification summarizes the results of experiments in mouse embryos lacking a functional *Nap1l2* gene, which is the mouse homologue of the human *NAP1L2* gene, as follows: "Taken together, these results suggest that the absence of *Nap1l2* function leads to an overproduction of cells in the neural tube and the surface ectoderm, and that this interferes with the proper histogenesis of these tissues." *Id.* at 53, lines 12-15. These results are provided in Figures 5 and 6, which depict mutant embryos with various developmental defects, including anencephaly, detached surface ectoderm, an open neural tube in the upper

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thoracic region, strong rearrangements of the brain, exposed neural tube and tissue, detached spinal chord, overproduction of surface ectoderm, and necrosis in the brain, which result from the absence of a functional *Nap1l2* gene. *See* Specification at 12, line 19 through pg. 14, line 4. Therefore, contrary to the Office's assertion that no specific biological activity or developmental defect is described in the specification, such activity and defects are clearly demonstrated in the specification.

Demonstration of the biological and developmental defects caused by the lack of a functional the *Nap1l2* gene in the embryo support the utility of the claimed invention. For example, as described in the specification an isolated polynucleotide comprising a functional *Nap1l2* gene (as claimed in claim 24) can be used in methods of screening for therapeutic compounds that are useful to alter or prevent developmental defects, such as spina bifida or anencephaly. *See* specification at 9, lines 12-20. Specifically, this sequence can be modified, *see* specification at 56, lines 5-10, and used to develop embryos that lack functional *Nap1l2* genes and display these defects, which are useful in the screening methods described in the specification.

Applicants assert that this utility is a substantial, credible, real world utility that meets the Office's requirements under the Revised Interim Utility Guidelines. 64 Fed. Reg. 71440, 71441 (1999). Accordingly, the rejection of pending claims 25, 34, 35, 40, and 46 under 35 U.S.C. § 101 should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph

The Office asserted that one of skill in the art would not know how to use the claimed invention because it is not supported by a credible or well established utility, and therefore, the Office rejected claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58,

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and 60-61 under § 112, first paragraph. *See* Paper No. 15, item 4. As explained above, the claimed invention does have a credible, substantial, and real-world utility, so the rejection on this basis is not sustainable. Applicants respectfully request that the rejection be withdrawn.

The Office also rejected claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58, and 60-61 for a lack of written description support for sequences, allelic variants, or molecules that include at least one modification that causes a loss of biological activity or that hybridize under stringent conditions, are chromosomes or parts of a chromosome, or comprise heterologous sequences that include at least 20 nucleotides of SEQ ID NO: 4. *See* Paper No. 15, item 5. Applicants have canceled claims 15, 17, 24, 26, 33, 56, 57, 60, and 61, thus obviating the rejection of them. Furthermore, none of the remaining claims recite sequences with modifications or allelic variants.

Reference to high stringency remains in claim 40 and new claim 62, and Applicants argue that there is written description support for an isolated polynucleotide that hybridizes under high stringency to the sequences recited. The specification provides the conditions for high stringency beginning on page 26, line 22, through page 27, line 5. As explained in the Revised Interim Written Description Training Examples, written by the Office and available at http://www.uspto.gov/web/offices/pac/writtendesc.pdf, "highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention." Therefore, there is written description support for the sequences that hybridize under highly stringent conditions in claims 40 and 62. In addition,

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because the conditions for moderate stringency are also provided in detail in the specification, one of skill in the art would know that Applicants had possession of the sequences that hybridize under these conditions as well. Applicants respectfully request that the rejection be withdrawn.

The Office rejected claims 15-19, 22, 24-26, 33-34, 40-41, 46-48, 56-58, and 60-61 under 35 U.S.C. § 112, first paragraph, for lack of an enabling disclosure of polynucleotides that are modified from SEQ ID NO: 4 to cause a loss of biological activity. Paper No. 15, item 6. As indicated in response to the rejection under 35 U.S.C. § 112, first paragraph, for a lack of written description, Applicants have canceled claims 15, 17-19, 22, 24, 26, 33, 56, 57, 60, and 61. Furthermore, claims 16, 25, 34, 40, 41, 46-48, and 58 do not recite modifications of SEQ ID NO: 4 that cause a loss of biological activity. Therefore, the rejection for lack of an enabling disclosure is obviated. Applicants respectfully request that the rejection be withdrawn.

The Office rejected claims 40 and 41 as not being enabled by the specification. *See* Paper No. 15, item 7. Applicants submit, herewith, a Declaration by Danielle Berneman, Director of Patents & Inventions Office of the Institut Pasteur. The Declaration states that the deposit was made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. Applicants submit that this Declaration satisfies the requirements of 37 C.F.R. § 1.801 - § 1.809.

In item 8, the Office rejected claim 40 under 35 U.S.C. § 112, second paragraph, for not identifying the terms plasmid "pBPX1 or pBPX2 or pBPX3" by a SEQ ID NO.

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See Paper No. 15, item 8. Applicants have amended claim 40 to indicate that the insert of pBPX1 is in SEQ ID NO: 4.

The Office rejected claims 24 and 40 under 35 U.S.C. § 112, second paragraph, because it considered the term "stringent hybridization conditions" to be indefinite. *See* Paper No. 15, item 9. Applicants have canceled claim 24, but new claim 62 is derived from original claim 24. New claim 62 and claim 40 now recite "high stringency" and Applicants respectfully traverse the rejection because the definition of this term is fully provided in the specification. On page 26, line 22, through page 27, line 5, the specification recites:

> Conditions of high stringency are as defined by the protocol of Chuch and Gilbert 1986, PNAS 81, 1991-1995: Church Buffer: 1mM EDTA, 0.5 M Na2HPO$_4$, pH 7.2, 7% SDS overnight at 65°C. Stringent washing: two times wash in 40 mM Na_2HPO_4, pH 7.2, 1% SDS (wash II) at 65°C.

Because of this complete description, Applicants assert that the claim term is not indefinite and that the rejection be withdrawn.

In item 10, claims 19 and 58 were rejected under 35 U.S.C. § 112, second paragraph, because the Office asserted that the term "derived from an immortal cell line . . . [or a] tumor derived cell line" is indefinite. *See* Paper No. 15, item 10. Claim 19 has been canceled, thus obviating the rejection, and the term "derived" has been deleted from claim 58. Therefore, Applicants request that this rejection be withdrawn.

The Office rejected claim 26 because it asserted that the claim is missing an essential element and therefore is incomplete. *See* Paper No. 15 at 11, item 12. Applicants have canceled claim 26, thus obviating this rejection, and request that it be withdrawn.

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35 U.S.C. § 102

Claims 15, 17, 24, 25, and 33 were rejected as being anticipated by Adams, et al. (clone EST27025; Accession no. AA324132). *See* Paper No. 15, item 13. The Office asserted that the sequence disclosed in this reference contains at least one modification that causes the loss of biological function of the *NAP1L2* gene, as provided in SEQ ID NO: 4. Applicants have canceled claim 17 and claim 15, from which claim 17 depended and which recited the limitation of "at least one modification of a *NAP1L2*" gene. Furthermore, Applicants have canceled claim 24 and added new claim 62, from which claim 25 now depends. New claim 62 does not recite "at least one modification of a *NAP1L2*" gene. Finally, Applicants have canceled claim 33. In light of these claim cancellations and amendments, the rejection under 35 U.S.C. § 102(b), in light of Adams, et al. is obviated and Applicants respectfully request that it be withdrawn.

Finally, the Office rejected claims 15-17, 24-25, 33, 40-41, and 56 as being anticipated by Chen et al. (clone bWXD759, accession no. AC004074), because it asserted that the sequence provided in this reference is 100% identical to SEQ ID NO: 4. *See* Paper No. 15, item 14. Applicants traverse this rejection for claim 16 and new claim 62 because the claims as amended specify that the claimed purified polynucleotide consists of the sequence in SEQ ID NO: 4. Chen et al. discloses a sequence that is 153,578 bases long, whereas SEQ ID NO: 4 is only 1,520 bases long. Therefore, Chen et al. does not anticipate the polynucleotide claimed in claims 16, 25, and 62. Furthermore, Applicants respectfully note that claims 40 and 41 do not recite SEQ ID NO: 4 and therefore are not anticipated by Chen et al. Finally, Applicants have

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canceled claims 15, 17, 24, 33, and 56. Therefore, Applicants request that the rejection under 35 U.S.C. § 102(b) in light of Chen et al. be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: October 31, 2003

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